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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/644,289	05/10/1996	MOLLY F. KULESZ-MARTIN	RPP:135D-US	4031

7590 06/02/2003

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	33

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	08/644,289	KULESZ-MARTIN, MOLLY F.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears n the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-19* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-11 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 3-6, 8-11, 15-19 are being examined.

This application contains claims drawn to an invention nonelected with traverse in Paper No.8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 15-16, 19 remains rejected under 35 USC 112, first paragraph, pertaining to lack of a clear written description for reasons already of record in paper No:31.

Applicant argues that more than enough description is provided, since the possible sequences are specifically taught and there are only 18 amino acids in the peptide of question, one can easily determine whether the particular sequence raises an antibody response without undue experimentation. Applicant argues that it is a simple matter to truncate the peptide from either or both ends and test the truncated peptide to determine whether it raises an antibody response.

Applicant's arguments set forth in paper No.32 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that claim 15 does not recite that the peptide would give rise to an antibody which is reactive with the p53as but not with p53, and thus the argument does

not apply to claim 15, and Applicant argues limitation not in the claim. The sequence in claim 15 encompasses a polynucleotide sequence of any length, and any structure, and function, provided a portion of it encodes the peptide of SEQ ID NO:1.

Further, due to the language "gene sequence" claims 15-16, 19 encompass a genomic DNA sequence, the structure of which is not disclosed in the specification.

REJECTION UNDER 35 USC 103

Claims 1, 3-4, 17 remain rejected under 35 USC 103 as being obvious over Han et al (of record), in view of Sambrook et al (of record), Hupp et al (of record), and Funk, WD et al (of record) for reasons already of record in paper No:31.

Applicant argues that Han et al do not teach incorporation of a full length p53as sequence into a plasmid and that the suggestion to look for incorporation of a full length p53as sequence into a plasmid is merely from the statement in Han et al that "more precise biochemical and biological characterization of AS-p53 protein along with R-p53 protein appear to be critical in future studies of p53 function in normal cells and oncogenesis". Applicant argues that there are literally thousands of ways one might proceed with "more precise biochemical and biological characterization". Applicant further argues that since Han et al do not actually form any proteins at all, formation of proteins based upon the disclosure of Han et al, with respect to p53as was speculative. Applicant asserts that whether or not the sequence containing inhibitors that prevent transcription or translation was not known, disclosed or suggested by Han et al. Applicant further asserts that it is classic hindsight to zeroing in on incorporation of a

complete p53as cDNA sequence into a plasmid as a way to proceed with "biochemical and biological characterization" without any other such suggestion in Han et al.

Applicant asserts that Sambrook et al do not cure this critical defect, since Sambrook et al is concerned only with DNA replication, not translation, and therefore hardly address the "biochemical and biological characterization" suggestion made in Han et al. Applicant asserts that one would not have known whether the p53as alternatively spliced cDNA could be transcribed and then translated to form protein until it was tried.

Applicant asserts that the teaching of Hupp et al and Funk does not cure these critical defects.

Applicant's arguments set forth in paper No.32 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's arguments, the expression of cloned sequences into proteins is conventional in the art. Sambrook et al clearly teach that expressing large amounts of proteins from cloned genes in plasmids is valuable to the purification, localization, and functional analysis of the proteins (p.17.2). Sambrook et al also teach that intact native proteins have been produced in large amount in *E. Coli* for functional studies, and describe methods and plasmid vectors for producing fusion proteins and intact native proteins in bacteria (p. 17.2, p.17.10-17.28, 17.36). Sambrook et al further teach that cloned genes are conventionally expressed using expression vectors and that expression of cloned proteins have been used to: (1) confirm the identity of a cloned gene by using immunological or functional assays to detect the encoded protein;

(2) produce large amounts of proteins of biological interest that are normally available in only limited quantities from natural sources; (3) to study the biosynthesis and intracellular transport of proteins following their expression in various cell types; (4)to elucidate structure-function relationships by analyzing the properties of normal and mutant proteins (para bridging pages 16.3 and 16.4)

Further, the existence of a full length p53as cDNA is known from the teaching of Han et al, because Han et al teach its predicted protein, as being prematurely terminated as compared to p53 protein, and having 9 amino acid shorter and differing in 25 amino acids at the C-terminus, as compared to p53 protein. Moreover, although Han et al do not directly teach the structure of a full length p53as cDNA, one of ordinary skill in the art could readily obtained it, in view of the available information concerning the alternative spliced site on wild type p53, the primers unique for p53as, and the source of RNA for the alternatively spliced RNA, as taught by Han et al. Thus the alternative spliced p53as is readily transcribed into mRNAs which are used by Han et al. The alternative spliced RNA of p53 taught by Han et al seems to be same the claimed p53as sequence, i.e., being different from the wild type p53 within the final 50 carboxy-terminal amino acids so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, wherein said negative regulatory domain must be activated in p53 or p53 to have active DNA binding, because, as evidenced by Hupp et al, it is the C-terminus that inhibits DNA binding of wild type p53, and removal of the 30 C-terminal amino acids or change in the conformation of the C-terminus would activate p53 DNA binding, suggesting that this

region plays a regulatory role in controlling p53 activity. Further, in view of the teaching by Hupp et al and Han et al, one would have expected that the AS-p53 taught by Han et al would have a different conformation at the C-terminus, and thus would be activated to bind to DNA, wherein the DNA binding sequence is the same as the sequence "AGGCATGCCT/ AGGCATGCCT", bound by activated wild type 53, as taught by Funk et al. In addition, one would have expected that the 25 C-terminal amino acids of the AS-p53 protein taught by Han et al would elicit an antibody which is specific for AS-p53 but not with p53, because said 25 C-terminal amino acids are different from the C-terminal amino acids of the wild type p53, as taught by Han et al.

Thus given the teaching of Han et al, that allows one to deduct the full length p53as sequence, and given the teaching of Sambrook et al concerning the expression of plasmid vectors containing genes of interest into intact native proteins, which is conventional, one would have expected that full length p53as sequence is readily transcribed and translated into proteins with a reasonable expectation with success.

The motivation is obvious, i.e. to obtain full length protein expressed by a plasmid containing full length p53as cDNA for studying the function of p53as, since the differences in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes and it is critical to include p53as in the study of the function of p53, as suggested by Han et al, and to study the function of an expressed protein, as taught by Sambrook et al..

2. Claims 5-6, 8-11 and 18 remain rejected under 35 USC 103 as being obvious over Han et al in view of Lee et al for reasons already of record in paper No.29.

Applicant argues that Han et al do not teach incorporation of a full length p53as sequence into a plasmid and that the suggestion to look for incorporation of a full length p53as sequence into a plasmid is merely from the statement in Han et al that "more precise biochemical and biological characterization of AS-p53 protein along with R-p53 protein appear to be critical in future studies of p53 function in normal cells and oncogenesis". Applicant argues that there are literally thousands of ways one might proceed with "more precise biochemical and biological characterization". Applicant further argues that since Han et al do not actually form any proteins at all, formation of proteins based upon the disclosure of Han et al, with respect to p53as was speculative. Applicant asserts that whether or not the sequence containing inhibitors that prevent transcription or translation was not known, disclosed or suggested by Han et al. Applicant further asserts that the extension of incorporation of a full length p53as sequence into a virus by combination with Lee et al is even farther afield. Applicant asserts that Lee et al suggest nothing at al concerning p53as, and is directed to incorporation of entirely different sequences into viruses for purposes unrelated to the function of p53as. Applicant asserts that viruses are discussed for no purpose of Han et al, and that the purpose of Han et al and Lee et al are clearly different and have different functions and there is no reasons to combine them except on the basis of hindsight, and even then the presently claimed invention is not suggested.

Applicant's arguments set forth in paper No.32 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the expression of cloned sequences into proteins using viral vector is conventional in the art. Lee et al teach expression of a gene in baculovirus vectors to produce large quantities of protein, and the importance and advantages to obtain intact, biochemically active proteins in large quantities for the investigation of the properties of the proteins, by using viral vectors (p.2, lines 40-45). Thus, not only Lee et al teach the technical feasibility of a reasonable expectation of success, Lee et al also teach a motivation to do so, i.e. to obtain intact, biochemically active proteins in large quantities for the investigation of the properties of the proteins.

Further, the existence of a full length p53as cDNA is known from the teaching of Han et al, because Han et al teach its predicted protein, as being prematurely terminated as compared to p53 protein, and having 9 amino acid shorter and differing in 25 amino acids at the C-terminus, as compared to p53 protein. Moreover, although Han et al do not directly teach the structure of a full length p53as cDNA, one of ordinary skill in the art could readily obtained it, in view of the available information concerning the alternative spliced site on wild type p53, the primers unique for p53as, and the source of RNA for the alternatively spliced RNA, as taught by Han et al. Thus the alternative spliced p53as is readily transcribed into mRNAs which are used by Han et al. The alternative spliced RNA of p53 taught by Han et al seems to be same the claimed p53as sequence.

Thus given the teaching of Han et al, that allows one to deduct the full length p53as sequence, and given the teaching of Lee et al concerning expression of genes incorporated in a viral vector into intact native proteins, which is routine in the art, one would have expected that full length p53as sequence is readily transcribed and translated into proteins with a reasonable expectation with success.

The motivation is obvious, i.e. to obtain full length protein expressed by a plasmid containing full length p53as cDNA for studying the function of p53as, since the differences in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes and it is critical to include p53as in the study of the function of p53, as suggested by Han et al, and to study the properties of an expressed protein, as taught by Lee et al.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

May 30, 2003